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Associations of Prenatal Urinary Bisphenol A Concentrations with Child Behaviors and Cognitive Abilities

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Background: Prenatal bisphenol A (BPA) exposure has been associated with adverse neurodevelopment in epidemiological studies. However, prior studies had limited statistical power to examine sex-specific effects, and few examined child cognition.

Objectives: We estimated the association between prenatal BPA exposure and child neurobehavior at 3 y of age in a prospective cohort of 812 mothers and their children.

Methods: We measured BPA concentration in urine samples collected at ~12 wk gestation among women enrolled in a 10-city Canadian cohort study. At approximately 3 y of age, we assessed children's cognitive abilities with the Wechsler Primary and Preschool Scale of Intelligence™–III (WPPSI-III) and two scales of the Behavior Rating Inventory of Executive Function–Preschool (BRIEF-P). Parents reported children's behavior using the Behavior Assessment System for Children–2 (BASC-2) and the Social Responsiveness Scale™–2 (SRS-2). We estimated covariate-adjusted differences in neurobehavioral outcomes with a doubling in BPA concentration and sex-specific associations.

Results: BPA was not associated with WPPSI-III scores; child sex did not modify these associations. The association between BPA and BRIEF-P scores was modified by child sex (BPA × sex p-values ≤ 0.03). For example, a doubling of BPA concentration was associated with 1-point (95% CI: 0.3, 1.7) poorer working memory in boys and 0.5-point (95% CI: −1.1, 0.1) better scores in girls. BPA was not associated with most BASC-2 scales; however, it was associated with more internalizing and somatizing behaviors in boys, but not in girls (BPA × sex p-values ≤ 0.08). A doubling of BPA concentration was associated with poorer SRS-2 scores [β = 0.3 (95% CI: 0, 0.7)]; this association was not modified by sex.

Conclusion: Prenatal urinary BPA concentration was associated with some aspects of child behavior in this cohort, and some associations were stronger among boys. https://doi.org/10.1289/EHP984

Introduction

Bisphenol A (BPA) is a high-production-volume chemical that is used to produce polycarbonate plastics and resins used in some food can linings, medical equipment, thermal receipts, and other consumer products (Chapin et al. 2008; Ehrlich et al. 2014). Exposure is ubiquitous among people in industrialized countries and is predominantly from diet (Casas et al. 2011; von Goetz et al. 2010). There is some evidence that prenatal BPA exposure may increase the risk of neurobehavioral disorders in children (Braun 2016; Chapin et al. 2008). Some experimental studies in rodents suggest that prenatal BPA exposure is associated with behavior problems and that these effects may be sex-specific (Rebuli and Patisaul 2015; Rosenfeld 2015); however, in other studies, no effects of BPA on rodent neurobehavior were observed (Rebuli et al. 2015). Prenatal exposure to BPA may increase the risk of neurobehavioral disorders by affecting thyroid or gonadal hormones or neurotransmitter systems, which are both necessary for proper brain development (Castro et al. 2015; Meeker et al. 2010; Romano et al. 2015). BPA may also affect the production or metabolism of gonadal hormones, which are an important determinant of sexually dimorphic brain development; thus, BPA may differentially affect neurodevelopment in males and females (Arnold 2009; Matthews et al. 2001; Zhang et al. 2011).

Several epidemiological studies have reported that maternal urinary BPA concentration during pregnancy is associated with adverse behavioral outcomes (Braun et al. 2011; Casas et al. 2015; Evans et al. 2014; Harley et al. 2013; Roen et al. 2015), whereas others have not (Miodovnik et al. 2011). The presence and direction of specific associations between BPA exposure and child neurobehavior has been heterogeneous in these studies. This variation may arise from differences in study design features and from misclassification of BPA exposure that is a result of the high within-person variability of urinary BPA concentrations (Braun et al. 2012). In addition, some studies have reported that child sex modifies the association between BPA and neurobehavior, but the modest sample size of these studies may have limited their statistical power to identify sex-specific associations. Finally, studies in animals show that gestational BPA exposure may affect specific aspects of cognition, such as memory and learning (Jašarević et al. 2013; Wang et al. 2014), but few studies have examined the relationship between prenatal BPA exposure and children's cognitive abilities (Braun et al. 2011; Casas et al. 2015).

To precisely estimate the potential neurotoxic effects of BPA exposure, we examined the relationship between maternal urinary

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BPA concentrations measured during pregnancy and children's behavior and cognitive abilities at 3 y of age in a prospective cohort study from Canada with follow-up data on 812 children.

Methods

Study Participants

We used data from the Maternal–Infant Research on Environmental Chemicals (MIREC) study, a prospective cohort that recruited 2,000 women in the first trimester of pregnancy from obstetric and prenatal clinics in ten cities (11 study sites) across Canada from 2008 to 2011 (see Arbuckle et al. 2013 for additional details about eligibility, recruitment, and follow-up). Briefly, eligibility criteria included having the ability to consent and communicate in English or French, being ≥18 y of age, having plans to deliver at a local hospital, and agreeing to participate in the cord blood collection component of the MIREC study. We excluded women who were carrying a fetus with a known malformation or abnormality and those with a history of major chronic disease, threatened abortion, and illicit drug use. Of the 8,716 women we approached to participate in MIREC, 5,108 (58.6%) were eligible, 1,983 (38.8%) consented to participate, and 1,910 had singleton live births. We conducted follow-up on 896 (46.9%) singleton children born to these women when the children were ∼3 y old.

This research was approved by ethics review boards from Health Canada and Sainte-Justine Centre hospitalier universitaire (CHU) and Quebec CHU research centers and by ethics committees at the participating hospitals. Potential participants were provided with information about the objectives and design of the study and were asked to sign the informed consent forms for both the prenatal and child follow-up portions of the study.

Prenatal BPA Exposure Assessment

We collected a single urine sample from women at an average of 12.1 wk gestation (range: 5.1–15 wk), aliquoted the sample, froze the aliquots at −20°C within 2 h of collection, and shipped them on dry ice to the MIREC coordinating center in Montreal, where they were stored at −30°C. Urine samples were shipped in batches to the Centre de Toxicologie du Québec, Institut National de Santé Publique du Québec for analysis. The total (conjugated + free) concentration of BPA was quantified using previously described analytic chemistry methods (Arbuckle et al. 2014). The limit of detection (LOD) for this method was 0.2 ng/mL, and we assigned values below the LOD a value of 0.1 ng/mL.

We accounted for individual variation in urine dilution by measuring urine specific gravity (SG) with a refractometer and standardizing urinary BPA concentrations using a formula adapted from Duty et al. (2005):

$$P_s = P_i\left(\frac{SG_m - 1}{SG_i - 1}\right)$$

where P_s is the SG-standardized BPA concentration, P_i is the observed BPA concentration for the i–th woman, SG_m is the median SG (1.013), and SG_i is the observed SG for the i–th woman.

Child Follow-up and Neurobehavioral Assessments

Among 1,910 singleton children, 896 (46.9%) from all 11 MIREC study sites participated in at least one component of our child follow-up at an average age of 3.4 y (range: 2.8–4.2 y). Among these children, almost all of them completed internet-based or paper-and-pencil assessments of neurobehavior and covariates ($n = 812$ with complete exposure and covariate data). Owing to limited resources, we conducted in-person assessments of neurobehavior on children from seven MIREC study sites ($n = 544$ with complete exposure and covariate data). This in-person visit typically occurred in the participant's home, where trained research personnel collected urine and blood from the child, administered questionnaires, measured child anthropometry, and administered several neurobehavioral instruments to the child. Variation in sample size arose from incomplete questionnaires (parents did not complete the surveys) or invalid administration of in-person tests (e.g., inadequate testing environment).

We chose the tests described below for two reasons. First, previous studies report that the traits they measure are associated with prenatal exposure to environmental chemicals, including BPA (Braun et al. 2011; Dietrich et al. 2005; Harley et al. 2013). Second, some of these tests assess omnibus features of child neurodevelopment (e.g., IQ), whereas other tests measure specific features of clinical disorders such as attention deficit hyperactivity disorder (ADHD) (e.g., externalizing) and autism spectrum disorder (ASD) (e.g., affect recognition) (Doyle et al. 1997; Loukusa et al. 2014).

The questionnaire-based assessment included the administration of the Behavioral Assessment System for Children–2 (BASC-2) and two subscales from the Behavior Rating Inventory of Executive Function–Preschool (BRIEF-P) to caregivers using an internet-based platform or paper-and-pencil versions. The BASC-2 is a valid and reliable 134-item assessment of children's problem behaviors in community and home settings (Reynolds and Kamphaus 2002). It provides three composite scores that measure children's total [Behavioral Symptom Index (BSI)], externalizing, and internalizing behavior problems, as well as seven clinical subscales measuring children's hyperactivity, aggression, anxiety, depression, somatization, atypicality, withdrawal, and attention. We assessed emerging metacognitive abilities in children by parent report using 27 items from the working memory and plan/organize subscales of the BRIEF-P, an instrument originally designed to measure children's executive function (Gioia et al. 2003). Women were not aware of their urinary BPA concentration when they completed questionnaires about their child's behavior.

During the in-person assessment, parents completed the Social Responsiveness Scale™–2 (SRS-2), and children were administered the Wechsler Preschool and Primary Scales of Intelligence™–III (WPPSI-III) and the Affect Recognition test from the NEPSY® (A Developmental NEuroPSYchological Assessment). The SRS-2 is a valid and reliable 65-item assessment of reciprocal social behaviors including interpersonal behaviors, communication, and repetitive or stereotypic behaviors (Bölte et al. 2008). The SRS-2 provides a summary scale of all these behaviors, two scales of behaviors related to the Diagnostic and Statistical Manual–V (DSM-V) diagnostic criteria for autism spectrum disorders, and five subscales measuring social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviors. During the in-home visit, we administered the WPPSI-III, a valid and reliable assessment of children's cognitive abilities (Wechsler 2002). Children completed the Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming subtests of the WPPSI-III in their home. Finally, we administered the Affect Recognition test of the NEPSY® during the in-home visit. This test assesses a child's ability to recognize emotions from photographs of children's faces; lower scores indicate that the child has poor visual attention, visual discrimination, or facial recognition (Korkman et al. 2007). Study staff always attempted to provide an ideal and standardized environment for administering the

WPPSI-III and the NEPSY® in the home; this included ensuring that the test area was well-lit, quiet, and free from distractions and interruptions.

We used software provided by the test publishers and U.S. population-based normative referent data to calculate full-scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ) scores for the WPPSI-III. Higher WPPSI-III scores indicate better cognitive abilities. We used these same methods to calculate T-scores for the BASC-2, the SRS-2, and the BRIEF-P. For these three tests, higher T-scores indicate more of the behavior or poorer functioning. Finally, we calculated scale scores for the Affect Recognition test of the NEPSY®: higher scores indicate better recognition of emotions.

Covariates

We assessed numerous factors that might confound the association between prenatal urinary BPA concentration and child neurobehavior. Trained interviewers administered standardized interviews during the first and third trimesters to assess maternal age at delivery, maternal race, maternal education, marital status, maternal employment, household income, self-reported smoking during pregnancy, alcohol consumption, multivitamin use, and parity. At the time of the child assessment, mothers completed standardized questionnaires or assessments that measured the duration of breastfeeding, parenting stress (Parenting Relationship Questionnaire), depressive symptoms (Center for Epidemiological Studies–Depression Scale 10), and self-reported delinquent behavior during adulthood. We also administered the Home Observation for the Measurement of the Environment (HOME) Inventory, a semi-structured interview that measures the quality and quantity of the caregiving environment (Bradley et al. 1988).

We identified confounders by using directed acyclic graphs (DAGs) to select variables that were associated with both urinary BPA concentration and at least one neurobehavioral outcome, but not those that were causal intermediates or colliders (see Figure S1). We used the same set of covariates for all analyses. We also considered adjusting for study site because urinary BPA concentrations and measurement of children's behavior or cognitive abilities might vary across the study sites.

Statistical Methods

We began our statistical analyses by describing the central tendency and distribution of maternal urinary BPA concentrations and children's BSI, FSIQ, and SRS total scores by covariates. We examined the shape of the relationship between $\log_2$-transformed urinary BPA concentration and neurobehavioral scores using 3-knot restricted cubic polynomial splines. We used multivariable linear regression to estimate the covariate-adjusted association between $\log_2$-transformed urinary BPA concentration and neurobehavioral scores. In addition, we examined quintiles of urinary BPA concentration in relationship to some neurobehavioral outcomes to characterize the dose–response relationship. We used product interaction terms between child sex and prenatal urinary BPA concentration to estimate sex-specific associations and to test the difference in these associations between boys and girls.

We examined the impact of adjusting for study site by comparing models that did not adjust for study site, that included study site as a covariate, or that used generalized estimating equations (GEEs) to account for study site. Ultimately, we did not adjust for study site because adjusting for this variable did not meaningfully change our results, and the models using GEEs produced imprecise results when we examined quintiles of BPA exposure because of small sample sizes at one study site. We examined the magnitude and precision of individual point estimates as well as the pattern of estimates across neurobehavioral tests rather than relying solely on statistical significance testing.

We conducted a series of sensitivity analyses to assess the robustness of our results to various confounder adjustments. First, we compared our results with and without adjustment for covariates that were measured at the child follow-up visit (maternal depression, parenting stress, breastfeeding duration, and delinquent behavior) because these covariates may not be associated with prenatal urinary BPA concentration. Second, we adjusted for maternal receipt of welfare support ($n = 18$) and child age. Third, among children who completed the in-person visit, we adjusted for daycare attendance and the HOME Inventory. To avoid potential selection biases, we made comparisons between models adjusted for our primary covariates and those adjusted for our primary covariates plus daycare attendance and the HOME Inventory among the subset of children who completed the in-person follow-up. We also examined whether our method of accounting for urine dilution influenced our results by comparing results of models that adjusted for creatinine as a covariate with those that used SG-standardized BPA concentrations. Finally, because urinary BPA and phthalate metabolite concentrations may be correlated because of shared exposure sources (e.g., diet), and prenatal phthalate exposure may be associated with adverse neurodevelopment, we adjusted for maternal urinary concentrations of mono-ethyl phthalate, mono-*n*-butyl phthalate, mono-benzyl phthalate, and the sum of three di-2-ethylhexyl phthalate metabolites (Factor-Litvak et al. 2014; Miodovnik et al. 2014).

Results

Compared with mothers whose children did not complete follow-up, mothers of children who completed follow-up at 3 y of age were more likely to be older, white, better educated, married or living with their partner, employed, nonsmokers during pregnancy, and to use folic-acid supplements during pregnancy (see Table S2). Baseline maternal covariates were not substantially different among women whose children completed the questionnaire-based follow-up vs. in-person follow-up. Median maternal urinary BPA concentrations were similar among women who did (0.8 ng/mL; 25th percentile: 0.3, 75th percentile: 1.6) and did not (0.9 ng/mL; 25th: 0.4, 75th: 1.8) complete follow-up.

Among mothers whose children completed follow-up, urinary BPA concentration during pregnancy ranged from <LOD to 79.1 ng/mL, and 86% of women had detectable concentrations. Median urinary BPA concentration did not substantially vary with covariates (Table 1). Mean BSI, SRS, and FSIQ scores were 51 [standard deviation (SD) = 7], 45 (SD = 6), and 107 (SD = 14), respectively. FSIQ scores were higher than the expected mean of 100, whereas SRS scores were lower than the expected mean of 50. Mean BSI, SRS, and FSIQ scores differed with several covariates. On average, FSIQ scores were lower and BSI and SRS scores were higher among children whose mothers were less educated, had lower household income, had greater parenting stress, and had more depressive symptoms.

We observed linear associations between prenatal urinary BPA concentrations and children's behavior or cognitive ability scores (results not shown, all nonlinear term p-values > 0.08 from spline models). Among all children and after adjustment for covariates, we observed few notable associations between prenatal urinary BPA concentration during pregnancy and children's BASC-2, BRIEF-P, WPPSI-III, and NEPSY® scores (Table 2). However, child sex modified the associations between prenatal

Table 1. Central tendency and variation of maternal urinary BPA concentration during pregnancy and child BASC-2 BSI, SRS total, and WPPSI-III FSIQ scores at 3 y of age according to covariates: MIREC study.

	BPA		BSI		SRS		FSIQ	
Variable	*n*	Median (25th, 75th)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Overall	812	0.8 (0.5, 1.5)	808	51 (7)	537	45 (6)	541	107 (14)
Maternal age, years								
18–25	26	1 (0.6, 2.2)	26	50 (4)	14	48 (7)	15	103 (12)
>25–35	493	0.8 (0.5, 1.5)	490	51 (7)	339	46 (6)	340	107 (14)
>35	293	0.8 (0.4, 1.3)	292	50 (7)	184	45 (6)	186	107 (14)
Maternal Race								
White	702	0.8 (0.5, 1.5)	700	51 (7)	462	45 (6)	462	108 (13)
Asian/Pacific Islander	27	0.5 (0.3, 1.2)	27	51 (6)	15	46 (5)	16	109 (11)
Other	49	0.8 (0.4, 1.4)	47	51 (8)	36	48 (6)	39	96 (14)
Multiracial	34	0.7 (0.4, 1.5)	34	50 (6)	24	46 (6)	24	107 (15)
Maternal education								
Graduate degree	229	0.7 (0.4, 1.3)	229	50 (6)	145	44 (5)	146	110 (12)
University degree	325	0.9 (0.5, 1.5)	324	51 (7)	221	45 (7)	222	108 (14)
Some college, trade school, or diploma	214	0.8 (0.5, 1.8)	211	51 (7)	147	46 (6)	148	103 (14)
High school or less	44	0.9 (0.4, 1.6)	44	51 (8)	24	47 (7)	25	99 (11)
Marital status								
Married or living with partner	791	0.8 (0.5, 1.4)	788	50 (7)	520	45 (6)	524	107 (14)
Not married or living alone	21	1 (0.7, 2)	20	54 (9)	17	49 (7)	17	101 (15)
Household Income (CAD)								
>100,000	330	0.8 (0.5, 1.3)	329	50 (7)	215	44 (6)	217	109 (13)
80,000 to 100,000	270	0.8 (0.4, 1.4)	269	51 (7)	175	45 (6)	176	106 (14)
40,000 to <80,000	136	0.9 (0.6, 2.1)	134	51 (6)	92	47 (7)	93	103 (14)
<40,000	76	1 (0.5, 1.9)	76	52 (8)	55	48 (6)	55	104 (14)
Employment								
No	93	0.9 (0.5, 1.7)	93	52 (8)	61	47 (9)	61	102 (17)
Yes	719	0.8 (0.5, 1.4)	715	50 (7)	476	45 (6)	480	107 (13)
Parity								
0	357	0.9 (0.5, 1.6)	355	51 (7)	236	46 (6)	239	108 (14)
1	332	0.7 (0.4, 1.4)	330	51 (7)	217	45 (6)	217	106 (14)
≥2	123	0.8 (0.5, 1.2)	123	50 (6)	84	45 (7)	85	103 (12)
Maternal smoking								
No	783	0.8 (0.5, 1.5)	779	51 (7)	521	45 (6)	525	107 (13)
Yes	29	0.8 (0.6, 1.5)	29	51 (9)	16	49 (7)	16	98 (16)
Prenatal alcohol use								
No	448	0.8 (0.5, 1.5)	445	51 (6)	306	45 (6)	309	106 (14)
Yes	364	0.8 (0.5, 1.4)	363	50 (7)	231	45 (6)	232	108 (13)
Prenatal folic acid supplement use								
No	534	0.8 (0.5, 1.5)	531	51 (7)	362	45 (6)	367	106 (14)
Yes	278	0.8 (0.4, 1.4)	277	50 (7)	175	45 (6)	174	108 (13)
Duration of exclusive breastfeeding, months								
≥6	416	0.8 (0.5, 1.3)	415	51 (6)	266	45 (6)	268	108 (13)
<6	396	0.9 (0.5, 1.6)	393	51 (7)	271	46 (6)	273	105 (14)
Parenting Stress								
Low	682	0.8 (0.5, 1.4)	681	49 (6)	448	44 (5)	450	108 (13)
High	130	0.9 (0.4, 1.7)	127	56 (7)	89	52 (8)	91	102 (17)
Maternal delinquency after high school								
No delinquent behaviors	662	0.8 (0.4, 1.4)	659	50 (6)	429	45 (6)	432	108 (14)
Any delinquent behaviors	150	1 (0.5, 1.7)	149	53 (8)	108	47 (7)	109	104 (14)
Maternal CES-D Score								
<16	785	0.8 (0.4, 1.4)	782	50 (7)	518	45 (6)	522	107 (14)
≥16	27	1 (0.8, 1.8)	26	54 (7)	19	48 (5)	19	107 (12)
Child sex								
Male	399	0.8 (0.5, 1.5)	397	51 (7)	262	46 (7)	266	104 (15)
Female	413	0.8 (0.4, 1.4)	411	50 (6)	275	44 (5)	275	109 (12)

Note: BPA, bisphenol A; BASC-2, Behavioral Assessment System for Children–2; BSI, behavior symptom index of the BASC-2; CES-D, Center for Epidemiologic Studies Depression Scale; FSIQ, full-scale IQ of the Wechsler Preschool and Primary Scales of Intelligence; MIREC, Maternal–Infant Research on Environmental Chemicals; SD, standard deviation; SRS, total T-Score from the Social Responsiveness Scale™; WPPSI-III, Wechsler Preschool and Primary Scales of Intelligence™, 3rd edition.

urinary BPA concentration during pregnancy and internalizing and somatization scores on the BASC-2, as well as working memory and plan/organize scores on the BRIEF-P (effect measure modification p-values < 0.10). In boys, each doubling in prenatal urinary BPA concentration was associated with more internalizing ($\beta = 0.5$; 95% CI: −0.1, 1.1) and somatizing ($\beta = 0.6$; 95% CI: 0.0, 1.2) behaviors as well as with poorer BRIEF-P working memory ($\beta = 1.0$; 95% CI: 0.3, 1.7) and plan/organize ($\beta = 0.6$; 95% CI: −0.1, 1.2) scores, whereas the associations were null or slightly inverse in among girls (Table 2).

For those BASC-2 scales exhibiting associations with prenatal urinary BPA concentration in boys, we further charac-terized the shape of the dose–response relationship using quintiles of prenatal urinary BPA concentration. Among boys, we observed a monotonic dose–response relationship between prenatal urinary BPA concentration and somatization score but not between prenatal urinary BPA concentration and internalizing, plan/organize, or working memory scores (Figure 1; see also Table S3). For example, the mean somatization score among boys increased monotonically across all 5 quintiles of prenatal urinary BPA concentration,

Table 2. Adjusted difference in behavioral and cognitive test score at 3 y of age with doubling in specific gravity standardized maternal urinary BPA concentrations during pregnancy: MIREC study.

Neurodevelopmental test	*n*	All children: β (95% CI)	Boys: β (95% CI)	Girls: β (95% CI)	BPA × Sex *p*-value
BASC-2 Summary Scales					
BSI	808	0.1 (−0.1, 0.4)	0.3 (−0.2, 0.7)	0.1 (−0.3, 0.4)	0.5349
Externalizing	808	0.0 (−0.4, 0.3)	0.1 (−0.4, 0.6)	−0.1 (−0.5, 0.4)	0.6268
Internalizing	806	0.1 (−0.3, 0.5)	0.5 (−0.1, 1.1)	−0.2 (−0.7, 0.3)	0.0817
BASC-2 Clinical Scales					
Hyperactivity	809	0.0 (−0.4, 0.3)	0.1 (−0.5, 0.6)	−0.1 (−0.5, 0.4)	0.7262
Aggression	808	0.0 (−0.3, 0.4)	0.2 (−0.4, 0.7)	0.0 (−0.5, 0.5)	0.6046
Anxiety	803	0.0 (−0.4, 0.5)	0.0 (−0.7, 0.8)	0.0 (−0.6, 0.6)	0.8772
Depression	808	0.3 (−0.1, 0.7)	0.5 (−0.1, 1.1)	0.2 (−0.4, 0.7)	0.3722
Somatization	808	0.0 (−0.4, 0.4)	0.6 (0.0, 1.2)	−0.5 (−1.0, 0.0)	0.0063
Atypicality	809	0.1 (−0.3, 0.4)	0.3 (−0.2, 0.9)	−0.1 (−0.6, 0.3)	0.1871
Withdrawal	806	0.2 (−0.2, 0.6)	0.0 (−0.6, 0.6)	0.4 (−0.2, 0.9)	0.3666
Attention	812	0.0 (−0.1, 0.2)	0.1 (−0.1, 0.4)	0.0 (−0.2, 0.2)	0.5395
BRIEF-P					
Working Memory	810	0.1 (−0.3, 0.6)	1.0 (0.3, 1.7)	−0.5 (−1.1, 0.1)	0.0009
Plan/Organize	812	0.0 (−0.5, 0.4)	0.6 (−0.1, 1.2)	−0.5 (−1.0, 0.1)	0.0258
WPPSI-III Summary Scales					
FSIQ	541	0.1 (−0.7, 0.9)	0.7 (−0.4, 1.9)	−0.3 (−1.4, 0.7)	0.1710
VIQ	538	−0.2 (−1.0, 0.5)	0.3 (−0.8, 1.4)	−0.7 (−1.7, 0.3)	0.1660
PIQ	536	0.6 (−0.3, 1.5)	1.1 (−0.3, 2.4)	0.2 (−1.0, 1.4)	0.3433
WPPSI-III Subtests					
Vocabulary	544	−0.1 (−0.2, 0.1)	0.1 (−0.2, 0.3)	−0.1 (−0.4, 0.1)	0.2259
Block Design	541	0.1 (−0.1, 0.3)	0.2 (−0.1, 0.4)	0.0 (−0.2, 0.3)	0.4635
Information	531	0.0 (−0.2, 0.1)	0.1 (−0.2, 0.3)	−0.1 (−0.3, 0.1)	0.2088
Object Design	541	0.1 (−0.1, 0.3)	0.2 (−0.1, 0.4)	0.0 (−0.2, 0.3)	0.3552
Picture Completion	541	0.1 (−0.1, 0.2)	0.2 (−0.1, 0.4)	0.0 (−0.2, 0.2)	0.2863
SRS-2					
Total	537	0.3 (0.0, 0.7)	0.5 (0.1, 1.0)	0.2 (−0.2, 0.6)	0.3090
Awareness	537	0.4 (−0.1, 0.8)	0.6 (0.0, 1.3)	0.2 (−0.4, 0.7)	0.3008
Cognition	537	0.3 (0.0, 0.6)	0.5 (0.0, 1.0)	0.2 (−0.3, 0.6)	0.4361
Communication	537	0.4 (0.0, 0.7)	0.5 (0.1, 1.0)	0.2 (−0.2, 0.6)	0.2777
Motivation	537	0.2 (−0.2, 0.6)	0.3 (−0.3, 1.0)	0.0 (−0.5, 0.6)	0.4628
Restricted	537	0.4 (0.0, 0.7)	0.4 (−0.2, 0.9)	0.3 (−0.2, 0.8)	0.8306
DSM Social	537	0.3 (0.0, 0.6)	0.5 (0.1, 1.0)	0.2 (−0.3, 0.6)	0.2174
DSM Restricted	537	0.4 (0.0, 0.7)	0.4 (−0.2, 0.9)	0.3 (−0.2, 0.8)	0.8353
NEPSY®: Affect Recognition	497	−0.1 (−0.2, 0.1)	0.1 (−0.2, 0.3)	−0.1 (−0.3, 0.0)	0.1620

Note: Adjusted for maternal race, education, age, marital status, employment, smoking during pregnancy, alcohol use during pregnancy, folic acid supplement use during pregnancy, parity, months of exclusive breastfeeding, parental stress, and depressive symptoms. Positive coefficients for the BASC-2, BRIEF-P, and SRS indicate that BPA concentrations are associated with more behavior problems. Positive coefficients for the WPPSI-III and NESPY indicate that BPA is associated with better performance. BASC-2, Behavioral Assessment System for Children–2; BRIEF-P, Behavior Rating Inventory of Executive Function–Preschool; BPA, bisphenol A; BSI, behavior symptom index of the BASC-2; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; FSIQ, full-scale IQ; MIREC, Maternal–Infant Research on Environmental Chemicals; NEPSY®, A Developmental NEuroPSYchological Assessment; PIQ, performance IQ; SRS, Social Responsiveness Scale™, 2nd Edition; VIQ, verbal IQ; WPPSI, Wechsler Preschool and Primary Scales of Intelligence™–III.

whereas internalizing scores were 2.4 points (95% CI: −0.1, 4.9) higher among boys in the fourth quintile than those among boys in the first quintile, but only 0.9 points (95% CI: −1.7, 3.5) higher among boys in the fifth quintile.

Each doubling in prenatal urinary BPA concentration during pregnancy was associated with higher scores on the SRS-2 among all children; the association was not modified by child sex (effect measure modification *p*-values > 0.22) (Table 2). Although SRS-2 scores tended to increase across prenatal urinary BPA quintiles, the increases were not consistently monotonic (Figure 2, see also Table S4). For example, children in the second, third, fourth, and fifth quintiles of prenatal urinary BPA concentration had DSM-V social behavior scores that were 0.8 (95% CI: −0.5, 2.2), 0 (95% CI: −1.0, 1.3), 1.2 (95% CI: −0.1, 2.6), and 1.5 (95% CI: 0.1, 2.9) points higher, respectively, than children in the first quintile. The associations between prenatal urinary BPA concentration and SRS scores related to social behaviors were stronger in boys than in girls, but the lowest sex × BPA *p*-value was 0.2174. Prenatal urinary BPA concentration was associated with poorer NEPSY®–II Affect Recognition score, but the 95% CI of the point estimate included the null value [β = −0.1 (95% CI: −0.2, 0.1)].

In sensitivity analyses, adjusting for covariates collected at 3 y of age, welfare receipt, child age, or HOME Inventory score generally did not appreciably change the results of our analyses for SRS scores or BASC-2 internalizing scores (see Figures S2 and S3). Although the association between BPA concentration and SRS scores was slightly attenuated after adjustment for welfare, the magnitude of these differences was ≤0.1 points. For example, after adjustment for welfare, the association between BPA concentration and Social Cognition score was 0.3 (95% CI: −0.1, 0.6), compared with 0.4 (95% CI: 0, 0.7) before adjustment. Associations between BPA concentration and internalizing or somatization score were unchanged when we accounted for urine dilution by adjusting for $\log_{10}$-transformed creatinine concentration (see Figure S3); however, the associations between prenatal urinary BPA concentration and SRS scores were attenuated but more precise when adjusting for creatinine compared with using SG-standardized concentrations (see Figure S2). Adjustment for phthalate concentration did not substantially alter the associations of BPA with internalizing or SRS scores (see Figures S2 and S3).

Discussion

In this cohort, we observed that prenatal urinary BPA concentration was associated with poorer parent-reported reciprocal social behaviors as measured by the SRS-2 among both boys and girls. Furthermore, we observed some sex-specific associations where increasing prenatal urinary BPA concentration was positively

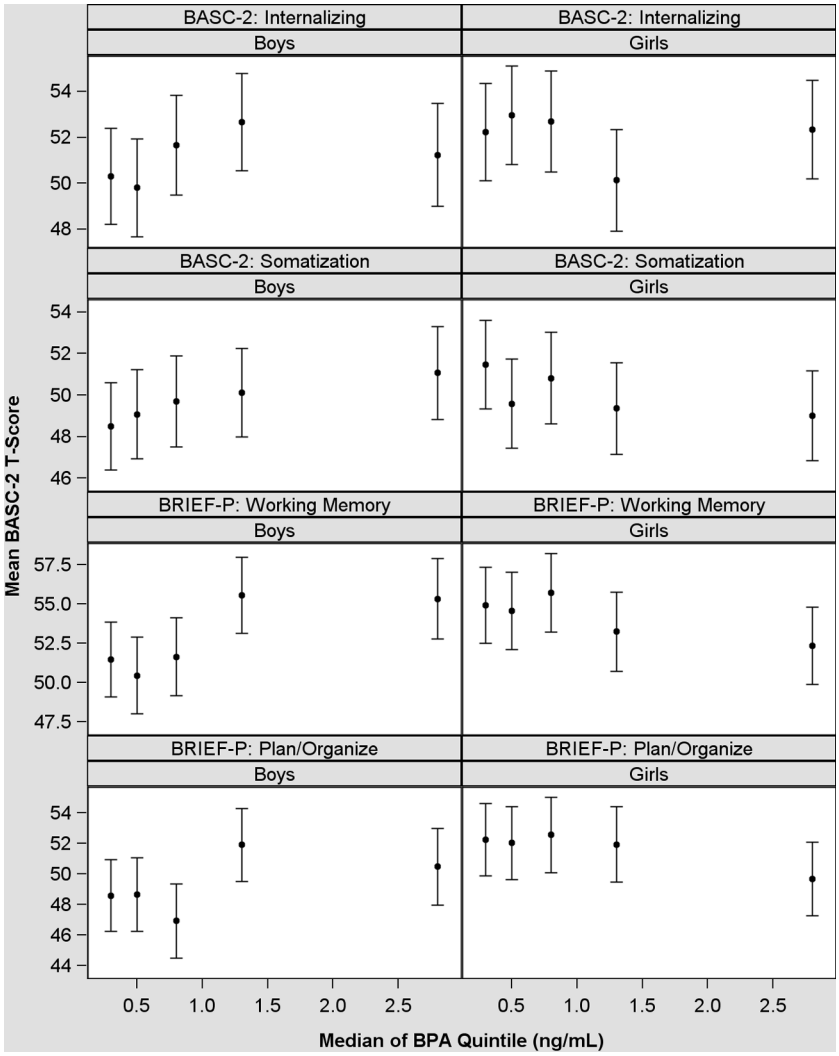

Figure 1. Covariate adjusted mean child BASC-2 and BRIEF-P scores by maternal urinary BPA quintile: MIREC Study. Adjusted for maternal race, education, age, marital status, employment, smoking during pregnancy, alcohol use during pregnancy, folic acid supplement use, parity, months of exclusive breastfeeding, parental stress, and depressive symptoms. Maternal urinary BPA concentrations are specific-gravity standardized. Quintile ranges were 0.1 to <0.4 ng/mL, 0.4 to <0.7 ng/mL, 0.7 to <1.0 ng/mL, 1.0 to <1.7 ng/mL, and 1.7 to 79 ng/mL. Error bars represent the 95% confidence intervals. $n = 806$, 805, 810, and 812 for internalizing, somatization, plan/organize, and working memory, respectively. Note: The *y*-axis scale changes in each row. BASC-2, Behavioral Assessment System for Children–2; BPA, bisphenol A; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool; MIREC, Maternal–Infant Research on Environmental Chemicals.

correlated with more parent-reported somatization and internalizing behaviors and poorer parent-reported working memory and planning/organizing skills in boys, but not in girls. The associations between maternal urinary BPA concentration during pregnancy and other measures of children's cognitive abilities and behavior at 3 y of age were largely null.

Our study adds to a number of modestly sized studies ($n = 137 - 438$) examining prenatal BPA exposure and child neurobehavior (Braun et al. 2011; Casas et al. 2015; Evans et al. 2014; Harley et al. 2013; Miodovnik et al. 2011; Roen et al. 2015). The sample size of the present study is a notable strength because it allowed us to more precisely estimate the presence and nature of sex-specific associations compared with prior studies. Consistent with the present results, four studies from three prospective cohorts reported that increasing prenatal urinary BPA concentration was associated with either internalizing or somatizing behaviors in children, with stronger associations in boys than in girls (Evans et al. 2014; Harley et al. 2013; Perera et al. 2012; Roen et al. 2015). In another cohort, prenatal BPA concentration was associated with more internalizing and externalizing behaviors in girls, but not in boys (Braun et al. 2009, 2011). Another study found that prenatal BPA concentration was associated with an increased risk of ADHD-related behaviors at 4 y of age, with stronger associations in boys (Casas et al. 2015).

Previous studies have not reported associations between prenatal urinary BPA concentration and cognitive outcomes in children (Braun et al. 2011; Casas et al. 2015). The findings of Casas et al. (2015) are consistent with our results of no association of prenatal BPA with child IQ or specific subtests of the WPPSI-III. Although we did observe an association of prenatal urinary BPA concentration with working memory and plan/organize scores in boys, a prior study using the BRIEF-P did not find an association (or modification by child sex) between prenatal urinary BPA concentration and working memory or plan/organize scores on the BRIEF-P (Braun et al. 2011).

Two prior studies reported that prenatal urinary BPA concentration was not associated with parent-reported reciprocal social behaviors and that these associations did not differ with respect to child sex (Braun et al. 2014; Miodovnik et al. 2011). In contrast, we observed poorer reciprocal social behaviors among

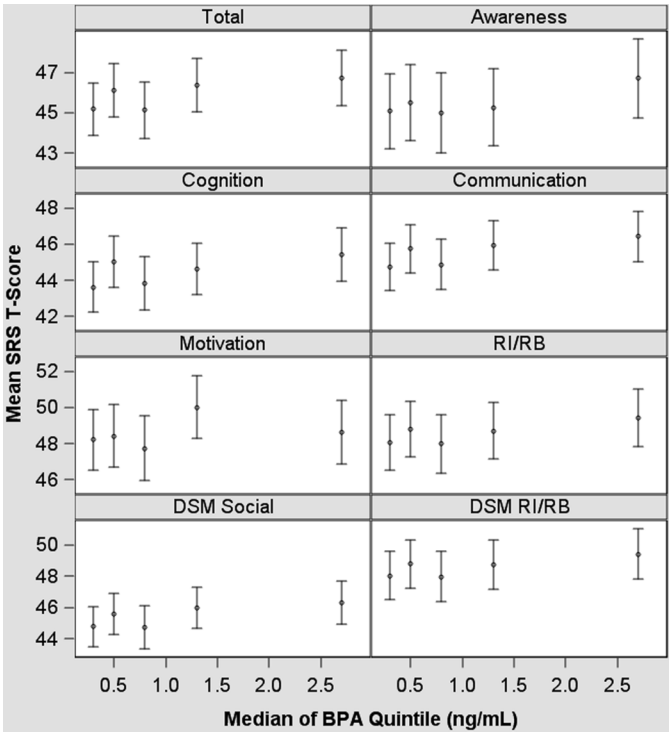

Figure 2. Covariate adjusted mean child SRS-2 scores by maternal urinary BPA quintile: MIREC Study ($n = 537$). Adjusted for maternal race, education, age, marital status, employment, smoking during pregnancy, alcohol use during pregnancy, folic acid supplement use, parity, months of exclusive breastfeeding, parental stress, and depressive symptoms. Maternal urinary BPA concentrations are specific-gravity standardized. Quintile ranges were 0.1 to <0.4, 0.4 to <0.7, 0.7 to <1.0, 1.0 to <1.7, and 1.7 to 79 ng/mL. Error bars represent the 95% confidence intervals. Note: The y-axis scale changes in each row. BPA, bisphenol A; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool; MIREC, Maternal–Infant Research on Environmental Chemicals; RI/RB, restricted interests/repetitive behaviors.

children born to women with higher prenatal urinary BPA concentrations. It should be noted that the associations between prenatal BPA concentration and SRS scores in this study were relatively modest, did not increase monotonically, and were typically largest in magnitude when comparing the fourth or fifth quintile with the first. There are several possible reasons for discrepant results across this and prior studies. First, urinary BPA concentration was lower among women in this study compared with most previous studies (median: 0.8 vs. $\sim 2\,\mathrm{ng/mL}$) and in contrast to prior studies, we may have not had sufficient BPA exposure variation to detect associations. Second, although the different neurobehavioral assessments used across studies could be a source of variation, it will depend on the specific instrument and domain. For instance, externalizing and internalizing scores on the BASC-2 and those on the Child Behavior Checklist tend to be highly correlated (Pearson $R > 0.68$); in contrast, for some clinical domains, such as anxiety, the correlations are lower (Pearson $R < 0.35$) (Reynolds and Kamphaus 2002). Third, the timing and number of prenatal urinary BPA measures during pregnancy could influence study results if there are periods of heightened vulnerability to BPA exposure. One animal study observed that BPA exposure during organogenesis and breastfeeding caused morphine-induced hyperlocomotion, preference for drug-paired place, and up-regulation of dopamine receptor function, whereas exposure at other gestational time periods did not (Narita et al. 2006). However, there does not appear to be an obvious pattern between the observed epidemiological results and the timing of exposure assessment in this and prior studies. Finally, the timing of the neurobehavioral assessment could influence study results for traits that change as children age (e.g., anxiety) (Merikangas et al. 2010). Thus, associations between early-life toxicant exposure and child neurobehavior may not manifest until later in life; this phenomenon has been observed for other neurotoxicants such as polybrominated diphenyl ethers and methylmercury (Chen et al. 2014; Karagas et al. 2012).

Given the episodic nature of BPA exposure and its short biological half-life (<6 h), there is substantial within-person variation of urinary BPA concentrations that makes accurate exposure assessment in epidemiological studies challenging (Braun et al. 2012; Thayer et al. 2015). Thus, nondifferential BPA exposure misclassification may be responsible not only for attenuation of observed associations but also for heterogeneity in the literature. Our study measured BPA in only one urine sample from each woman, and this likely led to misclassification of the women's BPA exposure. A simulation study found that the high within-person variation of a urinary biomarker such as BPA leads to associations being biased toward the null and that it might be necessary to obtain ≥10 repeated urine biomarkers from an individual or to analyze a pooled sample from each individual to limit bias in the effect estimate (Perrier et al. 2016). Other approaches, including regression calibration techniques, could be used to account for nondifferential exposure measurement error in studies with only a single estimate of exposure for all participants and repeated measures on a subset.

We were unable to examine potential mechanisms of BPA action in this study but could do so in the future using stored biospecimens available in the MIREC Study (Arbuckle et al. 2013). Prenatal BPA exposure may adversely affect a variety of biological processes during fetal development that are essential for proper neurodevelopment. In animal studies, BPA can affect the synthesis, action, transport, or metabolism of neurotransmitters, gonadal hormones, and thyroid hormones (Milligan et al. 1998; Tian et al. 2010; Zhang et al. 2011; Zoeller et al. 2005). BPA is a weak agonist of the nuclear estrogen receptors α and β and may affect androgen/estrogen concentrations by inhibiting key enzymes involved in steroidogenesis (Milligan et al. 1998; Zhang et al. 2011). The ability of BPA to act on gonadal hormones may explain the sexually dimorphic associations we and others have observed because gonadal hormones play an important role in neurodevelopment (Cohen-Bendahan et al. 2005). Other potential mechanisms of BPA action may include disruption of thyroid hormone homeostasis. In two epidemiological studies, prenatal urinary BPA concentration was associated with reduced neonatal thyroid stimulating hormone concentration, but the associations were observed in girls in one study and in boys in the other (Chevrier et al. 2013; Romano et al. 2015).

We observed relatively modest associations between prenatal urinary BPA concentration and specific aspects of child neurobehavior, particularly when considered from a clinical perspective. Despite this modest association, even subtle effects of BPA exposure could shift the distribution of continuous neurobehavioral traits to increase the risk of disorders such as autism spectrum disorders at the population level (Bellinger 2004). Indeed, Bellinger has shown that despite the modest associations between some environmental toxicants and neurobehavioral traits at the clinical level, the ubiquitous nature of these exposures results in effects at the population level that are comparable to or exceed the population-level effects of clinical risk factors (e.g., preterm birth or iron deficiency) (Bellinger 2012).

We comprehensively assessed numerous features of children's behaviors related to several neurodevelopmental disorders (e.g., anxiety, depression, ADHD, and ASD) and specific cognitive abilities. This is a notable strength because the majority of

previous studies have only examined child behavior. However, our assessment of children's behaviors, working memory, and planning/organizing was limited to parental reports and could be enhanced in future studies by employing objective or teacher-reported measures of these domains.

A limitation of our study is that we were unable to adjust for other predictors of child behavior and cognition, specifically parental behavior and cognitive abilities. We note that adjustment for our primary set of covariates modestly attenuated the association between prenatal urinary BPA concentration and children's SRS scores, but additional adjustment for maternal receipt of welfare, caregiving environment, or daycare attendance did not appreciably change these associations. Thus, although residual confounding by other determinants of child neurobehavior is possible, these other factors would need to explain additional variation in our outcomes beyond those variables we adjusted for in our models and be associated with prenatal BPA exposure.

Finally, we only assessed BPA exposure during the first trimester of pregnancy, whereas exposure during other periods of fetal development, infancy, or childhood might affect neurodevelopment. Some previous studies have reported that childhood urinary BPA concentration is associated with child behaviors (Harley et al. 2013; Tewar et al. 2016). Thus, identifying other periods of heightened vulnerability to BPA exposure in both the prenatal and postnatal periods remains an avenue of future research.

Conclusion

In the present study, maternal urinary BPA concentration during pregnancy was associated with some aspects of children's behaviors at 3 y of age: specifically, poorer reciprocal social behaviors among all children, more internalizing and somatization behaviors in boys, and poorer working memory and planning/organizing abilities in boys. Urinary BPA concentration during pregnancy was not associated with affect recognition, IQ, or externalizing behaviors, nor were these associations modified by child sex. Future investigations of early-life BPA exposure and child neurobehavior will need to reduce BPA exposure misclassification by conducting more extensive urine biomonitoring or by using measurement error correction methods.

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